5 Minute JournalClub

EORTC-06011: Low-Dose Decitabine versus Best Supportive Care for Elderly Patients with Intermediate- or High-Risk MDS

For more visit ResearchToPractice.com/5MJCMDSAML

Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

Acute myeloid leukemia (AML) and the myelodysplastic syndromes (MDS) account for approximately 20 percent of all hematologic cancer and related hemopathies diagnosed on an annual basis. Emerging and continuing clinical research has resulted in an increased understanding of the heterogeneous nature of these diseases and in the availability of novel treatment strategies and options. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in AML and MDS. To bridge the gap between research and patient care, this CME activity will deliver a serial review of recent key presentations and publications and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for AML and MDS.

LEARNING OBJECTIVE

- Appraise the benefits and risks of low-dose decitabine for elderly patients with intermediate- or high-risk MDS.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentation, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Gail J Roboz, MD
Associate Professor of Medicine
Director, Leukemia Program
Weill Medical College of Cornell University
NewYork-Presbyterian Hospital
New York, New York

Lecturing Honoraria: Celgene Corporation, Cephalon Inc, Eisai Inc, Genzyme Corporation.

Steven D Gore, MD
Professor of Oncology
Johns Hopkins University
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Baltimore, Maryland

Consulting Agreement and Stock Ownership: Celgene Corporation; Paid Research: Celgene Corporation, Johnson & Johnson Pharmaceuticals.

Hagop M Kantarjian, MD
Chairman and Professor, Leukemia Department
The University of Texas MD Anderson Cancer Center
Houston, Texas

Paid Research: Bristol-Myers Squibb Company, Genzyme Corporation, Novartis Pharmaceuticals Corporation.

EDITOR — Neil Love: Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Centocor Ortho Biotech Services LLC, Cephalon Inc, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Genzyme Corporation, GlaxoSmithKline, ImClone Systems Incorporated, Lilly USA LLC, Merck and Company Inc, Millennium Pharmaceuticals Inc, Monogram Biosciences, Novartis Pharmaceuticals Corporation, OSI Oncology, Roche Laboratories Inc, Sanofi-Aventis and Wyeth.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor.

This program is supported by an educational grant from Celgene Corporation.

Last review date: November 2009
Expiration date: November 2010

Click to go directly to our slides and comments on the **recent review of myelodysplastic syndromes**, **a new proposed prognostic model for MDS**, **the effect of pre-HCT azacitidine therapy on post-transplant outcomes**, **the efficacy of decitabine on survival in elderly patients with higher-risk MDS**, and a **comparison of three alternative azacitidine treatment regimens**.

As we were about to hit the send button on this, our latest e-blast, I happened to be on PubMed and stumbled across a just e-published (Nov 5) *New England Journal* **review article on myelodysplastic syndromes** (MDS). Thinking that the paper might be an important addition to this project, I quickly poured over the work. As usual, our entire clinical team loved the *NEJM* graphics (best in the business!), and the science behind this instant classic by Ayalew Tefferi and James Vardiman was spectacular. Further examination revealed only one prior (1999) *NEJM* review article on MDS, in which for example, there was but a brief mention of an initial 29 patient report of 5-azacitidine — the only reference to demethylating agents. Lenalidomide was nowhere to be found in this "ancient" document by Mark Heaney and David Golde. So at the last minute, we bypassed our usual formal faculty review and integrated this serendipitous discovery into the enclosed activity.

The concluding statements of these two review articles separated by 10 years reflect first a hopeful wish (1999): "The next decade will probably see a marked improvement in our ability to manage myelodysplasias as well as AML" and then confidence (2009): "Increasing information on the identity and nature of transformed hematopoietic stem cells and advances in biotechnology are helping to create the 'perfect storm' for breaking the current stalemate in our understanding of this disease."

So where are we today in MDS? Our faculty — Gail Roboz, Steven Gore and Hagop Kantarjian — once again comment on four papers that were identified and prioritized as important to clinical practice. The first addresses a proposed new **prognostic model for MDS** that accounts for such important factors as prior therapy and adverse cytogenetic profiles. The paper's author, Dr Kantarjian, believes this new system is superior to IPSS, but only time will tell.

Paper 2 comes out of the Moffitt Cancer Center and is a retrospective review of 54 patients receiving hematopoietic stem cell transplant (HCT) for MDS or chronic myelomonocytic leukemia (CMML). The outcomes of 30 patients receiving pre-HCT treatment with 5-azacitidine were compared to and found to be very similar to the

outcomes of 24 patients who did not receive this agent, leading the authors to conclude that 5-azacitidine can be safely and effectively used to stabilize patients prior to transplant.

The third study examines the other available demethylating agent, decitabine, and demonstrates that in spite of a 34 percent response rate, no improvement in overall survival (OS) was observed compared to supportive care in this well-conducted trial completed in Europe. While the lack of OS benefit in this study may relate to suboptimal duration of treatment, a recent US national Patterns of Care study conducted by our education group in preparation for an upcoming **ASH satellite symposium** demonstrated that 80 percent of oncologists using an up-front demethylating agent for MDS chose 5-azacitidine, perhaps reflecting the OS benefit reported with this agent.

Finally we have **a report of three alternative doses/schedules** of 5-azacitidine in MDS that through indirect comparison appear to be as effective and well tolerated as the approved day 1-7 regimen that requires weekend infusions. We may need a head-to-head trial to be fully convinced but it seems like a more patient-friendly regimen may in fact be out there.

The publications and presentations in this short series testify to significant forward momentum in MDS and AML. However, the ultimate hope is that 10 years from now, the next *NEJM* review article on MDS or AML will describe the unraveling and elimination of these diseases that have for so long resisted research progress.

Coming up next on 5-Minute Journal Club: a Phase II trial of up-front clofarabine in older patients with AML, a review of prognostic and predictive markers in AML, a trial of decitabine in older patients with AML and finally a retrospective review of more than 1,000 patients with AML and MDS receiving HCT demonstrating similar efficacy and toxicity patterns regardless of patient age, up to 78.

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates each of the five educational activities, comprised of a slide set with or without accompanying commentary, for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

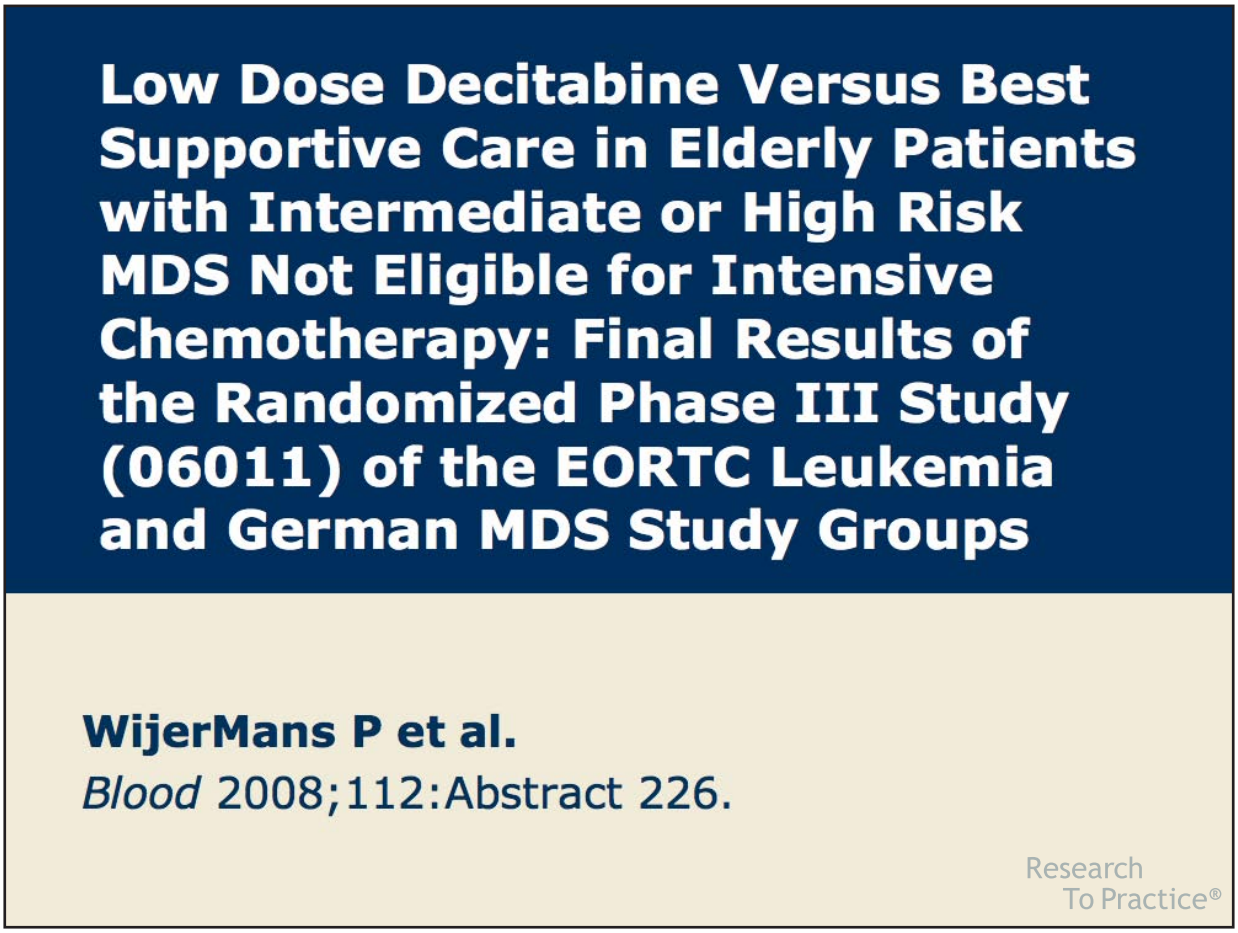
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

EORTC-06011: Low-Dose Decitabine versus Best Supportive Care for Elderly Patients with Intermediate- or High-Risk MDS

Presentation discussed in this issue:

WijerMans P et al. **Low dose decitabine versus best supportive care in elderly patients with intermediate or high risk MDS not eligible for intensive chemotherapy: Final results of the randomized phase III study (06011) of the EORTC Leukemia and German MDS Study Groups.** *Blood* 2008;**Abstract 226**.

Slides from the journal article and transcribed comments from recent interviews with Gail J Roboz, MD (10/6/09), Steven D Gore, MD (10/8/09) and Hagop M Kantarjian, MD (10/17/09) below



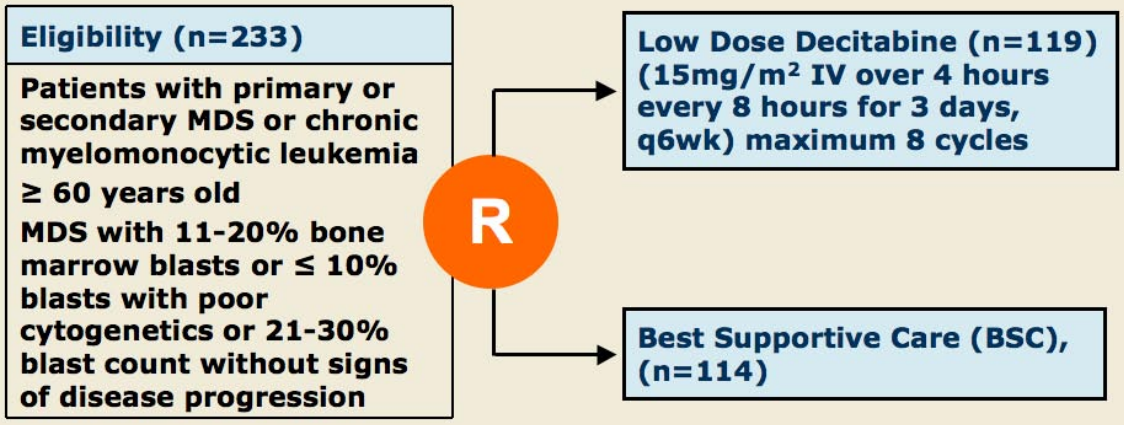
Introduction

- Decitabine has demonstrated efficacy in patients with myelodysplastic syndrome (MDS) using two different dosing regimens.
  - Low-dose decitabine therapy (15 mg/m^2 q 8 hours x 3 days every six weeks) has demonstrated improved efficacy over supportive care (ORR 17% vs. 0%, p<0.001) (*Cancer* 2006;106:1794).
  - An alternative outpatient regimen of decitabine (20 mg/m^2 q day x 5 every four weeks) demonstrated a response in 70% of patients according to modified International Working Group criteria (*Cancer* 2007;109:265).
- **Current study objectives (n=233):**
  - To assess the safety and efficacy of low-dose decitabine therapy versus supportive care in elderly patients with MDS who are not eligible for intensive chemotherapy.

Source: WijerMans P et al. *Blood* 2008;112:Abstract 226.

Research To Practice®

Phase III Randomized, Open-Label, Multicenter Trial of Low Dose Decitabine Versus Supportive Care



Patients stratified according to cytogenetics risk group, IPSS, primary or secondary MDS, and study center

Source: WijerMans P et al. *Blood* 2008;112:Abstract 226.

Research To Practice®

Patient Characteristics and Decitabine Treatment Courses

Patient Characteristics (n=233)	
Median age, n (range)	70 (60-90)
IPPS intermediate-2	55%
IPPS high	38%
Poor-risk cytogenetics	46%
Subsequent treatment therapy Transplant Induction chemotherapy	 10% 11%
Median number of decitabine cycles administered	4
Patients receiving ≤ 2 cycles of decitabine	40%

Source: WijerMans P et al. *Blood* 2008;112:Abstract 226.

Research To Practice®

Response: Decitabine Versus BSC in Elderly Patients with Intermediate/High Risk MDS

	Decitabine (n=119)	BSC (n=114)
Complete Response (CR)	13%	0%
Partial Response (PR)	6%	0%
Hematological Improvement (HI)[1]	15%	2%
Stable Disease	14%	22%
Overall Response Rate (CR+PR+HI)	34%	2%
Median Time to Response (CR/PR/HI)	0.32 yrs	
Response Duration	0.72 yrs	

[1]Patients in the decitabine arm with HI (n=18) showed the following responses: 3-lineage (n=7), 2-lineage (n=5), and 1-lineage (n=6).

Source: WijerMans P et al. *Blood* 2008;112:Abstract 226.

Research To Practice®

Survival: Decitabine Versus BSC in Elderly Patients with Intermediate/High Risk MDS

	Decitabine (n=119)	BSC (n=114)	Hazard ratio	p-value
Median OS (months)	10.1	8.5	0.88	0.38
Median PFS (months)	6.6	3.0	0.68	0.004
Median time to AML/death (months)	8.8	6.1	0.85	0.24

OS = overall survival; PFS = progression-free survival; AML = acute myelogenous leukemia.

Source: WijerMans P et al. *Blood* 2008;112:Abstract 226.

Research To Practice®

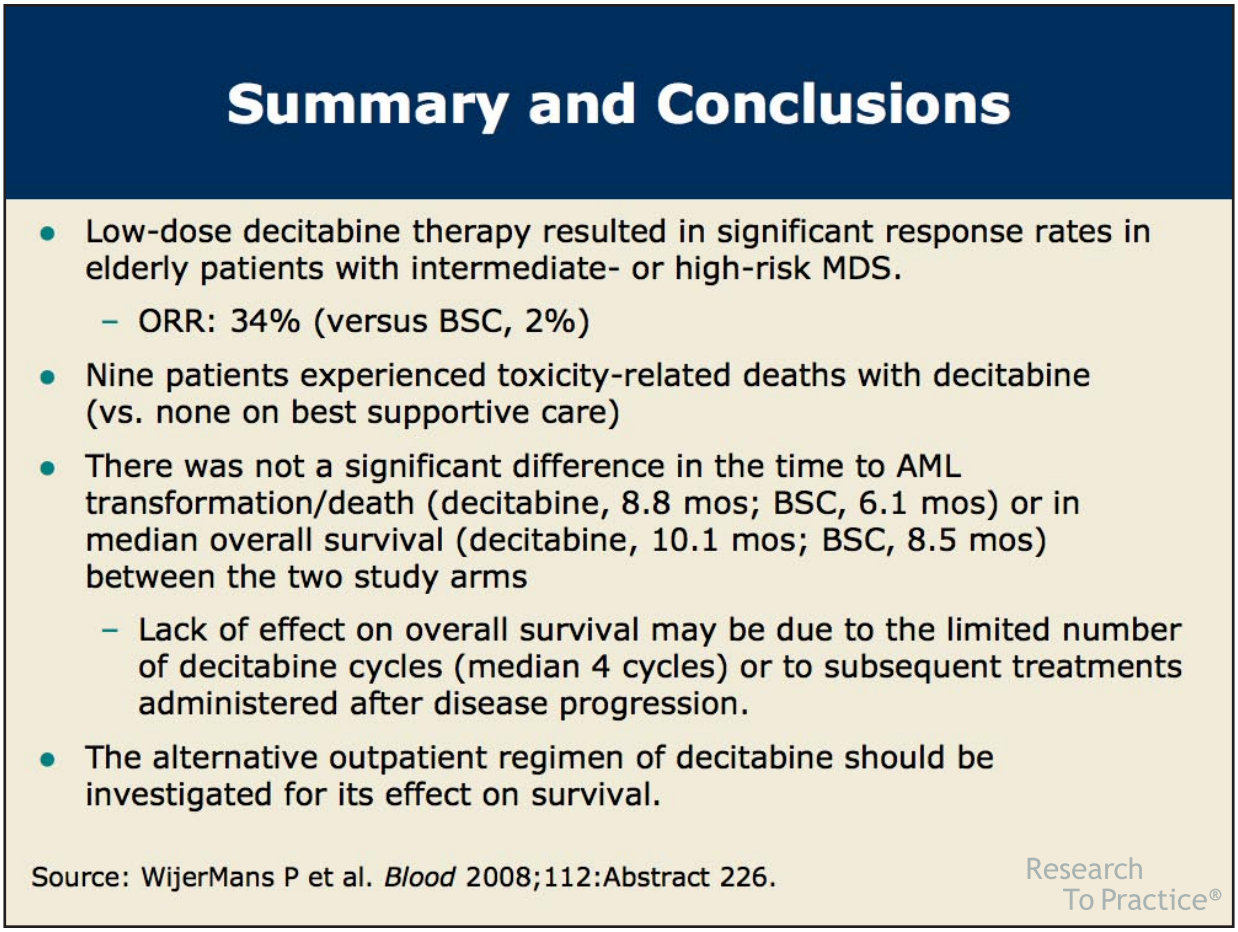
Adverse Events

Adverse Event	Decitabine (n= 119)	BSC (n=114)
Febrile neutropenia (Grades 3/4)	26%	7%
Infection (Grades 3/4)	59%	47%
Nausea (Grades 1/2)	28%	16%
Vomiting (Grade 1/2)	16%	9%

Toxicity-related deaths (n): Decitabine = 9, BSC = 0

Source: WijerMans P et al. *Blood* 2008;112:Abstract 226.

Research To Practice®



GAIL J ROBOZ, MD: This Phase III study showed a lack of survival benefit with low-dose decitabine over best supportive care, although it should be pointed out that the majority of patients did not receive multiple cycles of decitabine as received in the study with azacitidine. This highlights the need for repeated cycles over a longer period of time with the use of hypomethylating agents, in order to obtain the full benefit.

STEVEN D GORE, MD: This is a randomized trial that is similar to the azacitidine-001 study, but with decitabine versus best supportive care, in elderly patients with intermediate- or high-risk MDS. The FDA-approved treatment schedule for decitabine used in this study did not show a significant improvement in time to AML or death. I believe that these results, together with those from the AZA-001 study, establish the FDA-approved dose schedule of azacitidine as being the preferred treatment for patients with high-risk MDS. This is also acknowledged in the NCCN guidelines.

HAGOP M KANTARJIAN, MD: This study with decitabine was similar to the one with azacitidine versus conventional care. It has not been well publicized because the data were negative. In this study there were 233 patients with a median age of 70 years with the worst of the worst — patients with intermediate-2 and high-risk MDS. These patients were exposed to a dose schedule of three instead of seven days and courses were administered every six to eight weeks instead of every four weeks, with

a maximum number of eight courses. I believe that with an adverse-risk population, shorter and less frequent drug exposure and a shorter number of courses, it is not unusual that a survival benefit was not seen. Notice also that in the supportive care arm, the median survival was 8.5 months in contrast to 15 months in a previous study, suggesting that this is a population that is much worse than the one in the study of azacitidine versus conventional care.

Patients received a median of four cycles of decitabine, as opposed to the median number of nine cycles administered to patients in the study with azacitidine. Consequently, the CR rate is lower and the overall response rate is lower — in the range of 34 percent. There was significant prolongation of the progression-free survival, but the bottom line is there was no survival benefit, unlike with azacitidine.

Dr Roboz is Associate Professor of Medicine and Director of the Leukemia Program at Weill Medical College of Cornell University at NewYork-Presbyterian Hospital in New York, New York.

Dr Gore is Professor of Oncology at Johns Hopkins University in Baltimore, Maryland.

Dr Kantarjian is Chairman and Professor of the Leukemia Department at The University of Texas MD Anderson Cancer Center in Houston, Texas.